



When Susceptible Does Not Mean Treatable: Rethinking Tigecycline Reporting for Carbapenem-Resistant *Acinetobacter baumannii*

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Dear Editor,

Carbapenem-resistant *Acinetobacter baumannii* (CRAB) has narrowed therapeutic options and renewed interest in agents for which in vitro activity is easier to demonstrate than clinical effectiveness. Tigecycline is a notable example. A laboratory label of “susceptible” may be interpreted as a treatment recommendation even when the threshold has not been validated for the organism. Treatment nevertheless depends on the infection site, illness severity, achievable exposure, source control, and available alternatives (1). This manuscript and the proposed implementation and audit framework focus on confirmed CRAB. However, we recommend avoiding automatic tigecycline S/I/R assignment for all *Acinetobacter* spp. lacking an applicable recognized clinical breakpoint, irrespective of carbapenem susceptibility or testing platform (2-4). Method-specific limitations affect minimum inhibitory concentration (MIC) reliability and confirmation requirements, rather than providing the missing clinical breakpoint. Isolates identified only as the *A. baumannii*-calcoaceticus complex should retain that identification and should not be relabeled as confirmed *A. baumannii*.

Evidence was selected narratively through targeted web searches for PubMed-indexed studies and consultation of sources from the Clinical and Laboratory Standards Institute (CLSI), European Committee on Antimicrobial Susceptibility Testing (EUCAST), US Food and Drug Administration (FDA), and Infectious Diseases Society of America (IDSA). The searches and source consultation were completed on September 16, 2026. Search concepts

combined tigecycline and *Acinetobacter* with breakpoints, MIC testing, manganese, pharmacokinetics, mortality, and high-dose therapy. Sources were selected for their direct relevance to standards, analytical variability, or clinical interpretation; both unfavorable and qualifying findings were retained. This was not a systematic review, and the cited studies are illustrative rather than exhaustive.

The MIC measures inhibition of visible bacterial growth under specified test conditions. A clinical breakpoint links an MIC to a treatment category using microbiological, pharmacokinetic/pharmacodynamic (PK/PD), and clinical evidence for specified dosing and indications. An epidemiological cutoff (ECOFF) separates wild-type organisms from those with phenotypically detectable acquired resistance; it does not establish treatment success at a given dose or infection site (2-5). The EUCAST *A. baumannii*-tigecycline MIC distribution currently lists “ID” (insufficient data), rather than a numerical ECOFF; no wild-type/non-wild-type classification is proposed here (5). The MIC still provides useful quantitative microbiological information.

CLSI M100, 36th edition (2026), does not establish a tigecycline clinical breakpoint for *Acinetobacter* spp.; EUCAST version 16.1 lists “IE” (insufficient evidence), and FDA tigecycline criteria do not include *Acinetobacter* (2, 3, 6). The FDA MIC criteria of ≤ 2 , 4, and ≥ 8 mg/L apply to Enterobacterales for susceptible (S), intermediate (I), and resistant (R), respectively; applying them to CRAB is an unsupported cross-organism extrapolation (6). Terminology also differs: EUCAST uses I for “susceptible, increased exposure,” whereas FDA uses “intermediate” (3,

6). Neither an ECOFF nor a pharmacodynamic exposure threshold supplies the missing organism-specific clinical breakpoint (3-5).

The analytical result itself also requires caution. In a multicenter study of 1,105 *A. baumannii* isolates, Etest produced substantially more results above the investigators' borrowed threshold than broth microdilution, MicroScan, or Vitek 2 (7). A 2009 experiment demonstrated manganese-associated increases in Etest MICs on particular Mueller-Hinton agar preparations (8). This remains a mechanistic example of medium-dependent bias, not evidence that all contemporary media or automated systems have the same defect. These studies support method disclosure and local verification; their historical categorical comparisons do not validate a clinical breakpoint (7, 8).

Reference broth microdilution in cation-adjusted Mueller-Hinton broth should serve as the basis for MIC determination. EUCAST specifies freshly prepared medium on the day of tigecycline testing and appropriate quality control; commercial systems must be used according to their instructions and verified for the organism-drug pair (3, 4, 9). We propose reference confirmation when a nonreference result would determine tigecycline use in an invasive infection, when results conflict, or when an unexpected MIC or quality-control problem raises concern. Discrepancies exceeding one doubling dilution merit investigation; even a smaller difference may affect an individual decision. Laboratories should investigate purity, identification, media, and quality control; then issue the verified MIC and method in an amended report, retain the original result in the audit trail, and notify the treating team. Unresolved discrepancies should be disclosed, and isolates should be referred for expert testing.

This distinction also affects surveillance and stewardship. A borrowed category embedded in laboratory software may enter cumulative antibiograms or retrospective definitions of "appropriate" therapy. For CRAB-tigecycline, we propose retaining MIC distributions together with testing methods and avoiding an unqualified percentage of susceptible isolates. Research using a historical threshold should identify its source and state that it is not a validated CRAB breakpoint. Epidemiological classification requires an applicable, curated species-drug cutoff and must remain distinct from clinical susceptibility reporting (3-6).

Exposure concerns depend on both dose and infection site. Tigecycline distributes extensively into tissues, with relatively low circulating concentrations; therefore, a low MIC does not, by itself, support its use as sole therapy for CRAB bacteremia (1, 10). Approximately 22% of the administered dose is recovered unchanged in urine, but

this fraction does not establish adequate urinary exposure, and tigecycline is poorly suited to urinary infection (1, 10). Epithelial lining fluid exposure exceeded serum exposure in healthy volunteers, but these findings cannot establish adequate pulmonary exposure in critically ill patients with pneumonia (10). The same numerical MIC consequently has different therapeutic implications across bacteremia, pneumonia, and urinary infection. IDSA guidance identifies pharmacokinetic concerns when tigecycline MICs exceed 1 mg/L; this is an exposure-related warning, not a clinical breakpoint, and an MIC at or below 1 mg/L does not independently establish susceptibility or treatment success (1).

The licensed adult regimen is a 100-mg intravenous loading dose followed by 50 mg every 12 hours, with adjustment for severe hepatic impairment (10). The high-dose regimen discussed in CRAB guidance (200 mg followed by 100 mg every 12 hours) is off-label and does not establish reliable monotherapy efficacy. Current guidance from the IDSA favors sulbactam-durlobactam with a carbapenem for invasive CRAB and prefers minocycline when a tetracycline derivative is selected (1). Local availability and patient factors require specialist assessment. Tigecycline is not approved for hospital-acquired or ventilator-associated pneumonia, and its label includes an all-cause mortality warning (10).

Clinical observations illustrate uncertainty without validating an MIC threshold. In a mixed *Acinetobacter* cohort, 7 of 17 tigecycline-treated patients with secondary bacteremia and MICs ≤ 2 mg/L died within 14 days, compared with 9 of 65 patients receiving other agents (41.2% versus 13.8%) (11). Confounding by indication, baseline imbalance, and species heterogeneity prevent an unbiased estimate of the causal treatment effect and limit applicability to confirmed CRAB. This example neither proves tigecycline inferiority nor shows that a particular MIC predicts failure.

A meta-analysis of multidrug-resistant *A. baumannii* infections found no significant overall mortality difference, although microbiological eradication was lower with tigecycline and an in-hospital mortality subgroup favored comparators (12). The predominantly observational evidence, heterogeneity in infection sites, doses, and companion agents, and difficulty distinguishing colonization from infection limit interpretation. Studies predating contemporary CRAB regimens cannot establish their comparative effectiveness. These treatment comparisons also do not test whether changing laboratory wording improves outcomes.

More recent evidence remains mixed. A 2026 retrospective CRAB pneumonia study included 170 patients, with 62 per group after propensity score

matching. Thirty-day mortality was 43.5% with standard-dose and 56.5% with high-dose tigecycline ($P = 0.151$); microbiological success favored high dosing (50.9% versus 26.5%, $P = 0.012$) (13). Clinical success did not differ significantly, and adverse events were more frequent with high dosing. Residual confounding and selection of patients treated for at least 5 days limit inference.

The absence of a validated clinical breakpoint does not render a reliably determined MIC pharmacodynamically or clinically irrelevant. The MIC remains an input to quantitative exposure-response assessment, including the ratio of the area under the concentration-time curve to MIC (AUC/MIC) and the regimen-specific probability of target attainment (14). At a given exposure, a higher MIC reduces AUC/MIC; increasing the dose may improve target attainment, but does not establish efficacy at every infection site or create a susceptibility category. These assessments depend on MIC reliability, patient pharmacokinetics, infection-site data, and the applicability of the selected PK/PD target. They can inform specialist treatment decisions without independently validating a clinical breakpoint (3, 4, 14).

We therefore recommend reporting the numerical tigecycline MIC and testing method without automatic S/I/R assignment for *Acinetobacter* spp. lacking an applicable recognized clinical breakpoint. The following implementation framework focuses on confirmed CRAB and includes a suggested laboratory comment. This is a locally adaptable proposal, not a universally mandated statement or a validated clinical intervention. It is consistent with EUCAST's general advice to avoid categorical reporting when breakpoints are unavailable (4). Laboratory leadership must reconcile implementation with applicable regulations, accreditation requirements, approved device instructions, and institutional policies. If a categorical output is mandated, its interpretive source and limitations should be explicit, the exception should be documented, and specialist interpretation should be arranged; a borrowed category should not be presented as validated for CRAB.

"No CLSI, EUCAST, or FDA clinical breakpoint is established for tigecycline against *Acinetobacter* spp.; no S/I/R category is assigned. This MIC retains value for quantitative pharmacodynamic assessment but cannot independently predict treatment success. Interpret in the context of the infection site, dose, achievable exposure, and infectious diseases or antimicrobial stewardship advice."

The laboratory director should approve testing, confirmation, and reporting procedures jointly with infectious diseases and antimicrobial stewardship leads; the stewardship pharmacist should review dose, site,

companion therapy, and safety. We propose monthly audits of eligible reports without S/I/R assignment; triggered confirmations completed; treatment changes within 48 hours of release; monotherapy among tigecycline-treated invasive cases; and tigecycline courses judged appropriate for the infection site and achievable exposure. Each proportion should use all eligible reports, triggered tests, or treated courses as its stated denominator. Safety measures should include time to appropriate treatment, adverse events, and clinical deterioration. Exception records should include the reason, authorizer, interpretive rule, and clinical follow-up, and should undergo quarterly review. These proposed intervals and measures require local feasibility assessment and prospective evaluation.

Reporting tigecycline as susceptible for CRAB may imply a level of clinical certainty that is unsupported by applicable standards. Retaining the measured MIC, method, and interpretive limitation preserves useful information while acknowledging uncertainty. Whether this reporting approach improves prescribing or patient outcomes remains to be established.

Footnotes

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References

1. Tamma PD, Bonomo RA, Heil EL, Justo JA, Satlin MJ, Mathers AJ. Infectious Diseases Society of America 2026 guidance on the treatment of antimicrobial-resistant Gram-negative infections. *Clin Infect Dis*. 2026. ciag481. [PubMed ID: 42570093]. <https://doi.org/10.1093/cid/ciag481>.
2. Clinical and Laboratory Standards Institute. *Clinical and Laboratory Standards Institute*. Clinical and Laboratory Standards Institute; 2026,

- [cited 2026 Oct 18]. Performance standards for antimicrobial susceptibility testing. Available from: <https://clsi.org/shop/standards/m100/>.
3. European Committee on Antimicrobial Susceptibility Testing. *European Committee on Antimicrobial Susceptibility Testing*. EUCAST; 2026, [cited 2026 Sep 16]. Breakpoint tables for interpretation of MICs and zone diameters. Available from: https://www.eucast.org/fileadmin/eucast/pdf/breakpoints/v_16.1_Breakpoint_Tables.pdf.
 4. European Committee on Antimicrobial Susceptibility Testing. *European Committee on Antimicrobial Susceptibility Testing*. EUCAST; 2026, [cited 2026 Sep 16]. EUCAST guidance document on when there are no breakpoints. Available from: <https://www.eucast.org/bacteria/clinical-breakpoints-and-interpretation/when-there-are-no-breakpoints/>.
 5. European Committee on Antimicrobial Susceptibility Testing. *European Committee on Antimicrobial Susceptibility Testing*. 2026, [cited 2026 Sep 16]. MIC and zone diameter distribution website. Available from: <https://mic.eucast.org/>.
 6. Food and Drug Administration. *Food and Drug Administration*. 2026, [cited 2026 Sep 16]. Tigecycline – Injection products: FDA-identified interpretive criteria. Available from: <https://www.fda.gov/drugs/development-resources/tigecycline-injection-products>.
 7. Marchaim D, Pogue JM, Tzuman O, Hayakawa K, Lephart PR, Salimnia H, et al. Major variation in MICs of tigecycline in Gram-negative bacilli as a function of testing method. *J Clin Microbiol*. 2014;**52**(5):1617-1621. [PubMed ID: 24599978]. [PubMed Central ID: PMC3993642]. <https://doi.org/10.1128/JCM.00001-14>.
 8. Fernández-Mazarrasa C, Mazarrasa O, Calvo J, del Arco A, Martínez-Martínez L. High concentrations of manganese in Mueller-Hinton agar increase MICs of tigecycline determined by Etest. *J Clin Microbiol*. 2009;**47**(3):827-829. [PubMed ID: 19144806]. [PubMed Central ID: PMC2650928]. <https://doi.org/10.1128/JCM.02464-08>.
 9. European Committee on Antimicrobial Susceptibility Testing. *European Committee on Antimicrobial Susceptibility Testing*. EUCAST; 2026, [cited 2026 Sep 16]. Routine and extended internal quality control for MIC determination and disk diffusion as recommended by EUCAST. Available from: <https://www.eucast.org/bacteria/methodology-and-instructions/disk-diffusion-and-quality-control/>.
 10. Food and Drug Administration. *Food and Drug Administration*. Pfizer; 2025, [cited 2026 Sep 16]. TYGACIL (tigecycline) prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/021821s056lbl.pdf.
 11. Liou BH, Lee YT, Kuo SC, Liu PY, Fung CP. Efficacy of tigecycline for secondary Acinetobacter bacteremia and factors associated with treatment failure. *Antimicrob Agents Chemother*. 2015;**59**(6):3637-3640. [PubMed ID: 25824230]. [PubMed Central ID: PMC4432115]. <https://doi.org/10.1128/AAC.04987-14>.
 12. Ni W, Han Y, Zhao J, Wei C, Cui J, Wang R, et al. Tigecycline treatment experience against multidrug-resistant Acinetobacter baumannii infections: a systematic review and meta-analysis. *Int J Antimicrob Agents*. 2016;**47**(2):107-116. [PubMed ID: 26742726]. <https://doi.org/10.1016/j.ijantimicag.2015.11.011>.
 13. Özgen-Top Ö, Aysert-Yildiz P, Tekin-Taş Z, Arslan Ş, Erkan E, Özcan FZ, et al. Standard- versus high-dose tigecycline in pneumonia due to carbapenem-resistant Acinetobacter baumannii: A propensity score-matched retrospective study. *Infect Dis Now*. 2026;**56**(2). 105242. [PubMed ID: 41421451]. <https://doi.org/10.1016/j.idnow.2025.105242>.
 14. Xie J, Roberts JA, Alobaid AS, Roger C, Wang Y, Yang Q, et al. Population pharmacokinetics of tigecycline in critically ill patients with severe infections. *Antimicrob Agents Chemother*. 2017;**61**(8). e00345 - 17. [PubMed ID: 28607024]. [PubMed Central ID: PMC5527570]. <https://doi.org/10.1128/AAC.00345-17>.